Remarks

Claims 1-5, 11-13, 22, 23, 25, and 38-43 are currently pending. Claims 11, 12, and 13 have been amended to correct grammatical errors.

Claims 1-4 stand rejected under 35 U.S.C. §101. Claims 1, 22, 25, and 43 stand rejected under 35 U.S.C. §112. Claims 1-4, 12, 13, 22, 25, and 38-40 stand rejected under 102(b). Claims 5, 11, 22, 23, 25, 38, and 40-43 stand rejected under 35 U.S.C. 103(a). Applicants respectfully traverse the rejections.

Rejection Under 35 U.S.C. §101

The Examiner rejected Claims 1-4 under 35 U.S.C. §101 as directed to non-statutory subject matter. Specifically, the Examiner argued that "claims 1-4 as written, do not sufficiently distinguish over proteins as they exit naturally." Claims 1-4 have been amended to address this rejection. Claims 1-4 now refer to a substantially purified peptide. Support for this amendment can be found in the specification, for example, at Paragraph 63. The addition of the phrase "substantially purified" indicates the hand of the inventor in obtaining the peptide. Thus, claims 1-4 as amended are allowable under §101.

Rejections Under 35 U.S.C. §112

The Examiner rejected claims 1, 22, 25, and 43 under 35 U.S.C. §112, first paragraph, for failing to comply with the enablement requirement. Specifically, the Examiner argued that the specification "does not reasonably provide enablement for a peptide comprising a fragment of SEQ ID No: 1 without regard to the structure or function of the fragment."

Applicants respectfully note that, as explained in Paragraph 30 of the specification, the particular fragments of SEQ ID No: 1 that are embodied in the present invention are those that function, such as to increase the degree or rate of osteogenesis by BMP-2 in mammalian cells, or those that increase the degree or rate of calcification in vertebrate cells, specifically mammalian chondrogenic or osteogenic progenitor cells. Also, forms of BBP containing modified amino

acid sequences are embodied in the present invention to the extent that they function, such as to increase the residency time and/or activity of BMP-2 or other TGF-β homologues, as described in the specification. The term "fragments" as used in the claims refers to fragments that exhibit these functional characteristics. Methods of testing the degree or rate of osteogenesis and calcification as well as the residency time and activity of BMPs are described in the specification, such as in Examples 2 and 4.

The Examiner also argued that "it would require undue experimentation for the skilled artisan to use the full scope of the claimed invention" because of "the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art, and the quantity of experimentation needed." Applicants respectfully disagree with the Examiner's contention that one of skill in the art would be required to randomly pick a peptide comprising a fragment of SEQ ID No: 1 and test it for useful activity in order to practice the claimed invention. Rather, Applicants contend that the specification has provided direction as to which particular fragments of SEQ ID No: 1 would be expected to increase the rate or degree of osteogenesis or calcification. BBP is comprised of an amino acid sequence that is similar to the TGF-β/BMP-binding region of futuin. The amino acid sequence in SEQ ID No: 1 is also similar to the human TGF-β receptor II. The comparisons of SEQ ID No: 1, human TGF-β receptor II, and bovine futuin are set forth in Figure 3. This figure shows the similarities in the amino acid sequences of the peptides. One of skill in the art would be able to use this Figure as a guide to determine which peptide fragments would be functional as according to the present invention, and standard techniques to test for activity. Also, the specification explains that BBP has a B-T-B molecular motif, and that the growth-factor binding amino acids are believed to reside in the T-section of the peptide. The specification further explains that substitutions in this section of the peptide may be expected to have a greater effect on the activity of BBP. One of skill in the art would understand, based on the above descriptions, which fragments and modifications of SEQ ID No: 1 would be most likely to function as according to the present invention.

The Examiner rejected claims 5 and 41 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Specifically, the phrase "and one of BMP-2 or demineralized bone matrix" in claim 41 was cited as indefinite. Claim 41 has been amended to address this rejection such that the claimed implant additionally includes one of BMP-2 or demineralized bone matrix. Support for this amendment can be found in, for example, Paragraph 54 of the specification.

The phrase "molecules having sequence similarity to TGF-β" in claim 5 was cited as indefinite. The Examiner argued that an artisan would not be able to determine what additional or material limitations were placed upon the claim by this element. But Applicants respectfully contend that the specification does indicate which molecules having sequence similarity to TGF-β would be operative in the present invention. The specification explains that the amino acid sequence of the BBP peptide is similar to the TGF-β/BMP binding region of fetuin, and the binding region of fetuin is similar to the TGF-β II receptor. BBP thus binds BMP-2, and BBP increases the degree or rate of osteogenesis and the degree or rate of calcification. The specification explains that BBP may also bind other molecules having similar binding domains to BMP-2, such as other TGF-β proteins. One of skill in the art would understand that the molecules referred to in claim 5 as "having sequence similarity to TGF-β" would be those molecules that contain binding domains that are similar to the BMP-2 binding domains. Such proteins would for example be able to bind TGF-β receptor II and fetuin, so they would also be expected to bind BBP. Furthermore, one of skill in the art would understand that the molecules referred to in claim 5 as having "sequence similarity to TGF-β" would not only bind BBP but may also exhibit increased residency time and activity when combined with BBP. Therefore, those molecules "having sequence similarity to TGF-β" have been described in the specification such that one of skill in the art would understand the metes and bounds of this claim element.

Rejections Under 35 U.S.C. §102(b)

Claims 1-4, 12, 13, 25, and 40 stand rejected under 35 U.S.C. §102(b) as being anticipated by Keifer (U.S. Pat. No. 5,620,867). The Examiner contends that Keifer discloses a BMP that contains the same sequence as BBP and thus anticipates the claimed SEQ ID No: 1 and inherently anticipates the claimed effects of BBP. Applicants respectfully disagree with the

Examiner's view of Keifer's teachings. First, the protein that Keifer disclosed in Figures 3 and 5 is secreted phosphoprotein-24 (Spp-24), which is not a BMP. *See, e.g.*, Brochmann, E. J., *et al.*, *Bone morphogenetic protein-2 activity is regulated by secreted phosphoprotein-24 kd, an extracellular pseudoreceptor, the gene for which maps to a region of the human genome important for bone quality*, 58 Metabolism 644 (2009)("Brochmann 2009"). Keifer thus mischaracterized Spp-24 as a BMP. Keifer states that BMPs are known to induce bone growth and that the amino acid sequences disclosed in Figures 3 and 5 are characteristic of the BMP class. But the disclosed sequences are those of the Spp-24 protein, which regulates BMPs. *See, e.g.*, Brochmann, 2009, *supra*.

There is no evidence that Spp-24 increases the rate or degree of osteogenesis or calcification. Rather, studies have shown that the full length Spp-24 molecule, when combined with BMP, completely inhibits bone formation. *See* Brochmann, E.J., *et al.*, *Carboxy terminus of secreted phosphoprotein-24 kDa (spp24) is essential for full inhibition of BMP-2 activity*, 28 J. Orthopedic Research 1200 (2010)("Brochmann 2010); Brochmann 2009, *supra*; Sintuu, C., *et al.*, *Full-length bovine spp24 [spp24(24-203)] inhibits BMP-2 induced bone formation*, 26 J. Orthopedic Res. 753 (2008).

The rejected claims are drawn to a 19 amino acid sequence contained in Spp-24 that binds BMP-2 and functions, such as to increase the rate of osteogenesis or calcification. Applicants respectfully contend that Keifer does not teach a fragment of Spp-24 that binds a BMP and achieves the described functions in the specification. Applicants also respectfully contend that Keifer does not disclose the specific 19 amino acid sequence of Spp-24 that binds BMP and increases the rate of osteogenesis or calcification. One of skill in the art practicing the Keifer patent would create a composition containing Spp-24 that inhibits bone growth when combined with a BMP. This the exact opposite of the effect of the claimed invention.

The Examiner contends that Keifer discloses the use of BMPs along with pharmaceutically acceptable carriers to stimulate bone growth. As explained, the protein Keifer identified was not a BMP. There is no evidence that Spp-24 alone stimulates bone growth. Furthermore, there is nothing in Keifer that suggests that any fragment of Spp-24 can be

combined with BMPs to function as SEQ ID No: 1. Instead, Keifer discloses the use of purified BMP to screen for cartilage or bone growth inhibitors. Keifer '867 patent, col. 12:57-58. Thus, Keifer does not disclose all of the elements in the rejected claims, and does not anticipate them under 102(b).

Claims 1-4, 12, 13, 22, 25, and 38-40 stand rejected under 35 U.S.C. §102(b) as being anticipated by Price (WO 96/21006). The Examiner contends that Price teaches the protein Spp-24 and that the amino acid sequence of Spp-24 includes the claimed SEQ ID No: 1. The Examiner also contends that by disclosing the sequence for Spp-24, Price also inherently anticipates the claimed effect of the BBP peptide. Applicants respectfully disagree with the Examiner's interpretation of Price's teaching. Applicants respectfully contend that Price, like Keifer, teaches the use of the entire Spp-24 protein, not the BBP peptide portion of the protein. As discussed above, the full Spp-24 protein will act to completely inhibit BMP-2 activity. *See* Bochmann, 2009, *supra*; Bochmann 2010, *supra*; Sintuu, *supra*. In contrast, the claimed BBP peptide will increase BMP-2 activity. Price does not disclose the use of the specific 19 amino acid fragment comprising BBP that will function as SEQ ID No. 1. As such, Price does not anticipate the claimed peptide.

Further, Price discloses the use of the Spp-24 protein as a protease-inhibitor. Price '006 patent, col. 2:17-3:2, 4:2-4. Price discloses that Spp-24 can be used to control the process of bone resorption by halting the excessive actions of proteases that destroy bone in diseases like osteoarthritis. *See* Price '006 patent, col. 2:24-3:2. In contrast, the claimed BBP peptide binds to BMP and functions, such as to increase the rate or degree of osteogenesis or calcification. Thus, the claimed BBP peptide is believed to regulate a different bone development process than the Spp-24 protein disclosed by Price.

Rejections Under 35 U.S.C. §103(a)

Claims 5 and 11 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Price in view of Anderson (U.S. Pat. No. 6,322,786). The Examiner contends it would have been obvious for one of skill in the art to combine Spp-24 and BMP-2 based on Price's teaching of the

Spp-24 protein, which includes SEQ ID No: 1, and Anderson's teaching that BMP-2 when mixed with bone matrix carrier augments bone repair. Applicants respectfully disagree with the Examiner's characterization of the prior art teachings. As discussed above, Price teaches the use of the entire Spp-24 protein as a protease inhibitor that will act to control bone resorption. The Spp-24 protein, when used in its full length, will inhibit the activity of BMP-2. *See* Bochmann, 2009, *supra*; Bochmann 2010, *supra*; Sintuu, *supra*. Thus, if one of skill in the art combined the teachings of Anderson and Price, the result would be the total inhibition of BMP-2 activity. In contrast, Applicants' claimed combination of BBP and BMP-2 functions, such as to result in increased BMP-2 activity and an increase in the rate or degree or osteogenesis or calcification. Since the combination of the elements disclosed in Price and Anderson would not produce Applicants' claimed invention, the teachings of Price and Anderson do not render Applicants' claimed invention obvious. Furthermore, Anderson also does not disclose the specific 19 amino acid sequence that when combined with BMP-2 functions, such as to increase its activity. Anderson does not cure the defect of the Price reference. Thus, the combination of Anderson and Price does not render the claims obvious.

Claims 22, 23, and 38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Price in view of Anderson and further in view of Bentz (U.S. Publication No. 2003/0095993) and Macaulay (U.S. Patent No. 6,291,428). The Examiner contends that it would have been obvious at the time of Applicants' invention to make a composition comprising Spp-24 and BMP-2 as taught by Price and Anderson, and to modify that teaching by attaching Spp-24 and BMP-2 to a solid support as taught by Bentz and Macaulay. For the reasons discussed above, the combination of Price and Anderson does not disclose the claimed combination. Further, Bentz and Macaulay, in disclosing solid supports, do not cure the defects of the Price and Anderson references. As such, the combination of Price and Anderson further in view of Bentz and Macaulay does not render the claims obvious.

Claims 25, 40, 41, and 43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Price in view of Anderson and further in view of Macaulay. The Examiner contends that it would have been obvious at the time of Applicants' invention to make a composition comprising

Spp-24 and BMP-2 as taught by Price and Anderson, and to modify that teaching by making a substrate formed into the shape of a pin, screw, plate, or prosthetic joint, as taught by Macaulay. For the reasons discussed above, the combination of Price and Anderson does not disclose the claimed combination. Further, Macaulay, in disclosing substrates, does not cure the defects of the Price and Anderson references. Therefore, the combination of Price and Anderson further in view of Macaulay does not render the claims obvious.

Claims 25, 40, and 42 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Price in view of Anderson and further in view of Peterson (U.S. Pat. No. 6,200,606). The Examiner contends that it would have been obvious at the time of Applicants' invention to make a composition comprising Spp-24 and BMP-2 as taught by Price and Anderson, and to modify that teaching by making an implant further comprising osteogenic or chondrogenic precursors, as taught by Peterson. For the reasons discussed above, the combination of Price and Anderson does not disclose the claimed combination. Further, Peterson, in disclosing implants, does not cure the defects of Price and Anderson. Therefore, the combination of Price, Anderson, and Peterson does not render the claims obvious.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that Claims 1-5, 11-13, 22, 23, 25, and 38-43 are in allowable form, and the application is now in condition for allowance. Applicants request the Examiner to indicate all claims as allowable, and the pass the application to issue.

The Commissioner is authorized to charge any additional fees or credit any overpayments associated with this Amendment to Deposit Account 13-0206. Applicants further invite the Examiner to contact the undersigned representative at the telephone number below to discuss any matters pertaining to the present Application. The Examiner is requested to contact the undersigned if the Examiner has any questions concerning this Response, or if it will expedite the progress of this application.

Respectfully submitted,

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Date: November 22, 2010

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail addressed to Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on November 22, 2010.

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Kelly Walsh